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Systematic Review

Role of tumour markers in ascertaining prognosis of oral squamous cell carcinoma: A systematic review

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Abstract
Human oral cancer is a major cause of mortality in the third world countries, comprising of 40-50% of all malignancies in several parts of India and South East Asia. Tumour markers are substances that can be found in the body when cancer is present. They are usually found in the blood or urine. They can be products of cancer cells or of the body in response to cancer. Present paper is an attempt to discuss the utility and potentiality of various tumour markers in order to detect oral squamous cell carcinoma.
Keywords: Tumour, tumour markers, squamous cell carcinoma

Introduction

Human oral cancer is a major cause of mortality in the third world countries, comprising of 40-50% of all malignancies in several parts of India and South East Asia. Oral cancer is relatively less common in Western society-2.5% of all malignancies. The Indian scenario represents 19% of all malignancies in men and 7% of that in women [1].

Inspite of the fact that oral cavity is examined routinely and relatively frequently, majority of new cases of intraoral cancer are discovered only when patient becomes symptomatic. More than 60% of these cancers are in advanced stage when first detected and treatment results are often disappointing. The proximity of these tumors to the vital structures in the head and neck region makes treating them difficult and the results are often severely deforming.

More than 95% of malignant head and neck tumors are squamous cell carcinomas with many similar prognostic factors but varying clinical and therapeutic characteristics depending on the topographic site of origin. Due to the differences in anatomical site of origin, some tumors present symptoms during the early stages while others remain asymptomatic until an advanced stage is reached. In most cases the first symptom is the visible and palpable lymph node metastasis of the neck. However, even within the same anatomical site of origin and identical histological grade, individual tumors show marked prognostic variability.

Overall prognosis of patients with oral cancer remains poor, with overall survival rate following definitive treatment approaching 30% at 5years. Despite recent technological advances in surgery and radiotherapy and newer cytotoxic chemotherapy, prognosis of patients with squamous cell carcinoma of head and neck region has remained static. Treatment of such patients continues to pose challenge because of diversity of tumor behavior and serious impact of treatment related morbidity and treatment failure on quality of life[4]. It leaves us handicapped in successful management of oral cancer patients. Additional parameters are therefore required to classify the tumour more precisely in terms of its aggressiveness and biology. Hence in recent years many attempts have been made to overcome shortcomings of histopathological examination by finding out advanced methods which go beyond simple light microscope histology.

Some techniques are largely based on cytological and histological preparations while others employ chemical or functional analyses. The ultimate goal is to find reliable indicator of biologic potential of precancerous and cancerous lesions.

Various advanced methods employed are:

- Micronucleus test
- Stereological morphometry technique on light or electron microscopic level
- Histochemistry
- Image cytometry
- Flow cytometry
- Study of various tumor markers

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With the advancement in the field of molecular pathology several tumour markers associated with tumorogenesis have emerged [3]. These tumor markers may be proteins, enzymes, hormones, foetal serum components, cell surface components, cytoplasmic constituents etc.

Tumour markers are substances that can be found in the body when cancer is present. They are usually found in the blood or urine. They can be products of cancer cells or of the body in response to cancer. Most tumour markers are proteins.

Tumour markers can be defined as a biochemical substance indicative of neoplasia, ideally specific, sensitive and proportional to the tumour load. As tumour cells multiply, cancer spreads and tissue is damaged, these substances increase and leak into the blood stream. Tumour marker levels in the blood help to evaluate certain types of cancers.

Advances in analysis of molecular alterations in cells undergoing malignant transformation have revealed the mechanisms that led to the occurrence and progression of malignancies. The identification of individual molecules that are associated with malignant transformation has led to an ever increasing number of molecular markers that have been related to tumor stage and grading or indicative for prognosis and clinical course of the disease.

Tumour markers can be used to stage cancer, to indicate a prognosis, to monitor treatment, or in follow-up to watch for cancer recurrence. Changes in some tumor markers have been sensitive enough to be used as targets in clinical trials. When used for diagnosis, tumor markers are used in conjunction with other clinical parameters such as biopsy and radiological findings.

Markers for cell proliferation have been used for more than a decade as molecular indicators of malignancy without having shown a clear relation to the clinical behavior of the disease. However, a lot of knowledge about key molecules of cell cycle control and apoptosis has been acquired during recent years and other new areas of tumour biology such as matrix degradation, adhesion molecules, and immunologic tumour defense have been researched in depth.

These molecular markers play an important role in tumour progression and regression. They act, both as diagnostic and prognostic markers in oral squamous cell carcinoma [8]. Moreover molecular markers which are linked to malignant transformation may provide a non-surgical therapeutic approach by targeting these molecules through gene therapy.

Characterization of a malignant disease by tumor markers is expected to improve our understanding of variations in the clinical course of individual patients and help to estimate their prognosis.

Classification

The assessment of the potential malignancy of oral lesions clinically or from light microscopy examination of haematoxylin and eosin-stained tissue sections is not totally satisfactory and is likely to be improved by examination of more specific cellular changes. In recent years there have been a number of scientific approaches to the problem of precancerous lesions with the aim to establish a more fundamental biochemical basis of understanding. The search to such markers of potential malignancy has been a major goal in oral pathology as there is a need to identify those potentially malignant lesions that will truly progress to malignancy from the majority that will not. Unless a marker has a predictive value approaching unity it cannot be relied upon diagnostically to the exclusion of other data; unfortunately few if any of the current markers meet this criterion. It is also important to establish whether tissue changes in assessment of potentially malignant lesions are not simply phenomena associated with cell proliferation.

The various tumor markers can be grouped under the following heads.

Cellular markers

A) Cell surface markers

1) Carbohydrates
- Blood Group antigens(A,B,H)
- Sialosyl Tn & Tn
- Sialosyl N-acetyl lactosamine
- Le^x & Le^y

2) Squamous carcinoma antigen
- Ca-1
- TA-4
- SQM-1
- 3H-1
- Differentiation Antigen
  - MAbk-984
  - MAbk-928

3) Histocompatibility Antigen

B) Intracellular markers

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1) Cytokeratins, Fillagrins, Involucrins
2) Desmosomal proteins
3) Quantitative DNA
4) Arachidonic acid products and enzymes

C) Basement Membrane Markers
- Laminin
- Collagen IV

D) Matrix Markers
- Tenacin

Molecular markers

A) Markers of cell cycle progression & proliferation
- Epithelial Growth Factor Receptor
- Cyclins
- Bcl-2
- Skp-2(S-phase kinase associated protein 2)
- Telomerase
- Uridine phosphorylase
- Thymidine phosphorylase
- Ki-67
- PCNA
- STAT-3
- MDM2
- Survivin
- WNT
- Id protein
- Cox-2
- AgNOR

B) Markers of tumor suppression & antitumor response
- pRB
- p 53
- cyclin dependent kinase inhibitor (CDK1)
  - p21
  - p16
  - p14
  - p27
- PTEN
- Bax
- Fas/Fas L
- S-100/S-100 A_2
- TGF β
- FHIT
- TNF-α
- P-12

C) Markers of angiogenesis
- VEGF/VEGF-R
- NOS II
- Pd- ECGF
- CD 34
- CD 105
- Fibrin & IL -8
- FGF-2

D) Markers of tumor invasion & metastasis
- MMP
- TIMP
- Syndecan-1

Review

I. Markers of cell cycle progression and proliferation

Normal cells require exogenous growth signals to stimulate proliferation. Growth stimuli include soluble and membrane bound growth factors, interactions with the extracellular matrix and cytokines. Typically these growth signals are transduced from cell surface receptors that subsequently activate multiple intracellular signaling pathways, resulting in cell proliferation [1].

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Mutation of proteins within these signal transduction pathways has disastrous consequences. If the message is altered, the cell may get a false message to proliferate, leading to cancer. For this reason, the genes of many signal transduction proteins were first discovered in their role as oncogenes before their functions in normal cells were elucidated.

Oncogenes are growth promoting regulatory genes that govern the cells' signal transduction pathways, and mutation of these genes leads to either overproduction or increased function of the excitatory proteins. Although oncogenes alone are not sufficient to transform epithelial cells, they appear to be important initiators of the process, and are known to cause cellular changes through mutation of only one gene copy.

'Oncogene' is a misnomer as the normal function of the genes does not involve oncogenesis, and in normal cells the genes are termed as proto-oncogenes. The proto-oncogenes are conserved through evolution in nature, and form essential components of the innate normal cell metabolic process involving, cell differentiation and apoptosis. [9] The genes code for functional and regulatory proteins including growth factors, growth factor receptors, protein kinases, nuclear transcription factors, and cell signaling proteins. Under normal conditions, proto-oncogenes are accelerators while tumor suppressors are the brakes in cell proliferation, and proper cell cycling is due to the two working together. The various mechanisms resulting in deregulation of such proteins leading to human cancers, primarily involves amplification, mutation, translocation or gene rearrangement, as well as deletion of normal allele. The oncogenes have a definitive role in oral cancer as reviewed in the following section.

1. Epidermal growth factor receptor (EGFR)

The epidermal growth factor receptor (EGFR; ErbB-1; HER1 in humans) is the cell-surface receptor for members of the epidermal growth factor family (EGF-family) of extracellular protein ligands [2].

The EGFR gene (ErbB-1) maps to 7p13-q22, encodes a receptor involved in cell signaling which is a trans-membrane tyrosine-specific phosphokinase which binds several ligands, including EGF, transforming growth factor alpha (TGF-α), amphiregulin, heparin-binding EGF-like growth factor, betacellulin, cripto and epiregulin, activating intracellular signaling via protein tyrosine kinase [4].

The epidermal growth factor receptor is a member of the ErbB family of receptors, a subfamily of four closely related receptor tyrosine kinases: EGFR (ErbB-1), HER2/c-neu (ErbB-2), HER 3 (ErbB-3) and HER 4 (ErbB-4). Mutations affecting EGFR expression or activity could result in cancer [2].

The known natural ligands of EGFR include EGF and TGF-α. After binding one of its ligands, EGFR forms a dimer with another EGFR molecule, and these receptors auto phosphorylate, leading to a cascade of intracellular signaling events, including activation of the Ras/Raf/mitogen activated protein kinase (MAPK), phosphatidylinositol-3-kinase (PI3K), Janus kinase (Jak), signal transducer and activator of transcription (STAT), and protein kinase C (PKC) pathways. These signaling pathways, in turn, mediate multiple functions, including cell proliferation and survival, invasion, metastasis and angiogenesis [1].

Increased EGFR signaling activity can occur through any of several mechanisms, including receptor overexpression due to gene amplification or transcriptional up-regulation, receptor mutation, or autocrine activation by overproduction of ligands. The most common mutation of EGFR is a truncation mutation, EGFR variant III (EGFRvIII), which is observed only in cancer cells and leads to constitutive activation of the receptor without ligand or receptor overproduction. In squamous cell carcinoma of head and neck, it has been detected in 42% of 33 tumors [1].

R. TODD *et al*. (1991) Detection of cellular sources of EGFR synthesis revealed that the basal cells in normal and hyperplastic human oral epithelium contained similar cellular levels of EGFR mRNA while the dysplastic and carcinomatous human oral epithelium contained significantly higher cellular levels of EGFR mRNA. The dysplastic and carcinomatous oral epithelium, which showed elevated cellular levels of EGFR mRNA, also corresponded to areas of altered growth pattern, as revealed by H3 mRNA in situ hybridization [3].

Scully *et al*. (1993) concluded from their study that there is EGFR overexpression in most oral and other head and neck carcinomas. EGFR gene amplification was found in less than 30% [5]. Gene amplification was not the primary reason for the increased EGFR expression in carcinomas but, rather messenger RNA (mRNA) over expression or receptor protein overproduction could be responsible. It was stated that all epithelial cells possess both low and high affinity EGFR; it is mainly the high affinity EGFR that appeared to be increased in tumourigenic cell lines [4].

Nam Hoon Cho *et al*. (2003) reviewed that epidermal growth factor receptors (EGFRs) are expressed on normal cells, at 20,000 to 200,000 receptors per cell, with the exception of hematopoietic cells, which do not express EGFRs. It is stated that, EGFRs may be present in much higher numbers on malignant cells. Binding of ligands, epidermal growth factor and TGF-α, to EGFR, induced receptor dimerization, leading to a cascade of cellular events ultimately resulting in DNA synthesis, cell proliferation, maturation, survival and apoptosis. While additional biological responses to EGFR activation resulted in the proliferation of cancer cells and the enhancement of metastatic potential. They too agreed that, the expression of EGFR is mainly regulated at the transcription level. An idea was concieved that EGFR mRNA production can be stimulated directly or indirectly by treating cells with EGF, dexamethasone,

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thyroid hormone, retinoic acids, interferon-α, or wild-type p53. EGFR overexpression was believed to be due to upregulated positive transcription factors or inactivated transcriptional repressors and was usually associated with poor prognosis. In their comparative study between p63 and EGFR the neoplastic squamous cells revealed strong but variable EGFR expression, and a part of the marginal cytoplasm of invading nests showed strong EGFR immunoreactrivity. However, koilocytotic atypia in CINs were never stained for EGFR. Overall, EGFR expression was 26.6% (44.0 vs 56.0%; EGFR-negative vs EGFR-positive groups) and showed no significant difference in the nonkeratinizing and keratinizing SCC groups (30.0 vs 33.8%) [6].

Masayuki Shiraki *et al*., (2005) examined the impact of immunohistochemical expression of p53, cyclin D1 and epidermal growth factor receptor (EGFR) markers on tumor progression in 140 oral cancers and found that p53, cyclin D1 and EGFR were expressed in 64 cases (46%), 54 cases (39%) and 54 cases (39%), respectively, but there was no inter-relationship between any two of these markers. None of these markers, including EGFR, had no significant impact on survival so they have concluded that Simultaneous coexpression of these markers in oral cancers might prove to be a useful indicator for identification of low- or high-risk patients [7].

Gracia-Caballero T *et al*., (2007) concluded that EGFR is a useful indicator of biological tumor behaviour, the high prevalence of EGFR overexpression suggests the possibility of anti-EGFR therapy in oral squamous cell carcinomas [10].

Alfredo A. *et al*. (2008) cited that many human cancers expressed high levels of growth factors and corresponding receptors, and many malignant cells exhibited highly active receptor tyrosine kinases due to their activation by an autocrine or paracrine mechanism, or by activating mutations in their coding sequence. EGFR overexpression represents an independent prognostic marker correlating with increased tumor size, decreased radiation sensitivity, and increased risk of recurrence. The elevated levels of EGFR expression leads to the activation of their kinase activity by spontaneous dimerization. Constitutive EGFR activation in HNSCC is also caused by its autocrine stimulation through the co-expression of EGFR with one of its ligands, TGFα, which is frequently observed in HNSCC and correlates with a poor prognosis. Moreover G protein coupled receptor induced cleavage of EGF like growth factors leading to EGFR transactivation and EGFR-related signaling in cancer cells, suggesting that GPCR-EGFR cross-communication may play a role in the development and progression of HNSCC and other human cancers [8].

2. Cyclins

Cyclins are a family of proteins involved in the progression of cells through the cell cycle.

A cyclin forms a complex with its partner cyclin-dependent kinase (Cdk), which activates the latter's protein kinase function.

Cyclins are so named because their concentration varies in a cyclical fashion during the cell cycle; they are produced or degraded as needed in order to drive the cell through the different stages of the cell cycle [11].

When its concentrations in the cell are low, the cyclin detaches from the Cdk, inhibiting the enzyme's activity, probably by causing a protein chain to block the enzymatic site [12, 13].

Kushner J *et al*., (1999) concluded that there is overexpression of cyclin A and cyclin B1 proteins in oral carcinoma. Furthermore, the poor correlations for cyclin B1 scores with other cell cycle indices suggest that there may be aberrant cell cycle progression at the G2/M checkpoint in oral carcinomas [14].

Mineta *et al*. (2000a) explained that cyclin D1 overexpression was associated with more aggressive tumor behavior and a worse prognosis than tumors that did not overexpress cyclin D1 [15].

Chen Q, *et al*., (2001) suggested that cyclin A may contribute to the progression of oral cancer and correlated to some degree with that of the p53 gene activity [16].

Chen HM *et al*., (2003) their results indicated that overexpression of cyclin A protein is associated with tumor progression and patient prognosis for oral squamous cell carcinoma [17].

Thomson PJ *et al*., (2006) concluded from their study that cyclin A is synthesized during S phase (its appearance coinciding with the onset of DNA synthesis) and is required for both S phase progression and for passage from G2 into mitosis. Overexpression was related to increased proliferative activity, increased populations of S phase cells, rapid cell growth and ultimately tumor development via unbridled cell proliferation with poor clinical outcome suggesting a definite role for cyclin A measurement as a predictive tool in clinical management of oral squamous cell carcinoma [18].

Thus, Cyclin A allows for an accurate evaluation of tumor progression and is an accurate indicator of poor prognosis.

Cyclin A expression can be detected using immunohistochemistry on both paraffin and frozen sections.

3. Bcl 2/Bcl XL

Bcl-2 was first described in follicular lymphoma that beret 14:18(q32, q21) translocation; this structural chromosomal aberration leads to overproduction of Bcl-2 messenger RNA and protein. Bcl-2 is localized at outer mitochondrial and the nuclear membrane, as well as at endoplasmic reticulum. Bcl-2 is known to

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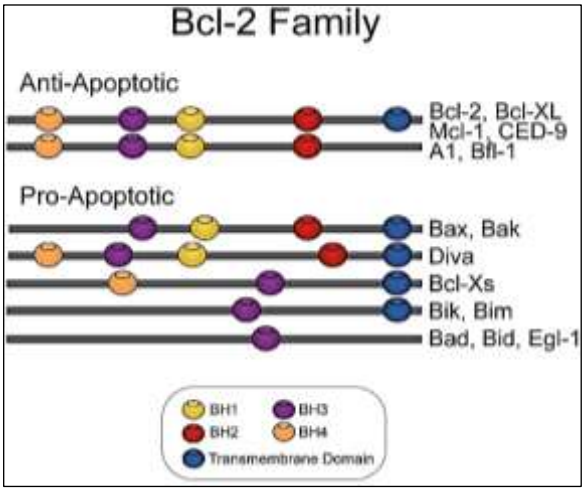
belong to a family of apoptosis-regulatory gene products that may be either death antagonists (e.g. Bcl-2, Bcl-X_L, and Mcl-l, AI) or death agonists (e.g. Bax Bak, Bcl-X_s, and Bad). The Bcl-2 oncoprotein inhibits apoptosis and is expressed by many tumors including carcinoma of the breast, cervix, and head and neck [19].



Apoptosis means programmed cell death; it is a genetically determined process and playing an active role in tissue size regulation, morphogenesis, and removing damaged cells that could be potentially dangerous for their host. Several agents involved in apoptosis regulation such as Bcl-2 family component act as an oncogene involved in oral carcinogenesis. Cancer occurs when mutation affects the control mechanisms of apoptosis and cell survival. The Bcl-2 gene was identified as blocking apoptosis because of its abnormal overexpression in follicular lymphoma [20].

Abnormal expression of Bcl-2 protein, usually in terms of overexpression in genetically modified cells such as tumor cells, contributes to the expansion of the damaged clone by preventing cell turnover because of programmed cell death, leading to cellular immortalization. Increased expression of the Bcl-2 protein can be detected in about 50% of human cancers, further emphasizing the importance of deregulating apoptosis as a fundamental step in human carcinogenesis. By promoting cell survival, Bcl-2 facilitates the permanent acquisition of mutations and malignant transformation; moreover, increased Bcl-2 protein expression in cancer cells possibly reflects tumor cell resistance to apoptosis and may have implication for their responsiveness to treatments [21].

Expression of Bcl-2 proto-oncogene was first seen in B-cell Hodgkin's lymphoma. Bcl-2 might directly contribute in oncogenesis shown by McDonnell *et al*. Elevated levels of Bcl-2 are seen in patients with chronic lymphocytic leukemia. Bcl-2 expression has been reported in many malignant diseases such as prostatic carcinoma and small lung carcinoma. The role of Bcl-2 gene product is to inhibit apoptosis which occurs in a variety of circumstances and to greatly increase their resistance to apoptosis by inducing anticancer drugs effect. Mitochondria and cell surface receptors mediate the two main pathways of apoptosis, the mitochondrial pathway is thought to be important in response to cancer treatment and is mediated by Bcl-2 family protein, and the final execution of cell death is performed by caspase cascade, which is triggered by release of cytochrome c from mitochondria [20].

Bcl2 expression during progression of oral squamous cell carcinoma are controversial. Some groups have shown an increased expression of Bcl2 in dysplastic lesions and in oral squamous cell carcinoma, others detected a sporadic or lack of expression.

Friedman M *et al*., (1997) reported that the overexpression of Bcl-2 in early lesions with a cure rate of 50%, as opposed to the generally expected 90%, suggesting that Bcl-2 is a significant prognostic indicator in early squamous cell carcinoma of head and neck.

Xin Xie *et al*. (1999) in their study investigated the level of spontaneous apoptosis and expression of the apoptosis- related proteins Bax, Bcl-2, and p53 in a series of tongue SCC, found a high Bax expression which correlated significantly with high values for the AI, whereas no correlation was found between the levels of expression of Bcl-2 and AI. Bax expression emerged as the most important single, i.e., not composite, prognostic marker, whereas high expression was associated with good prognosis when compared with low expression. Their study revealed that high expression of Bcl-2 was significantly associated with poor prognosis and low expression with good prognosis [22].

Yuen AP *et al*. (2002) concluded that Bcl-2 expression played a minor role in oral squamous cell carcinoma. And Bcl-2 expression had no significant correlation with tumour grade, stage and nodal metastasis stating that Bcl-2 expression is of no prognostic value on survival for patients treated by primary surgery [24].

Loro LL *et al*. (2002) determined bcl-2 and bax gene expression in oral epithelial dysplasias in relation to

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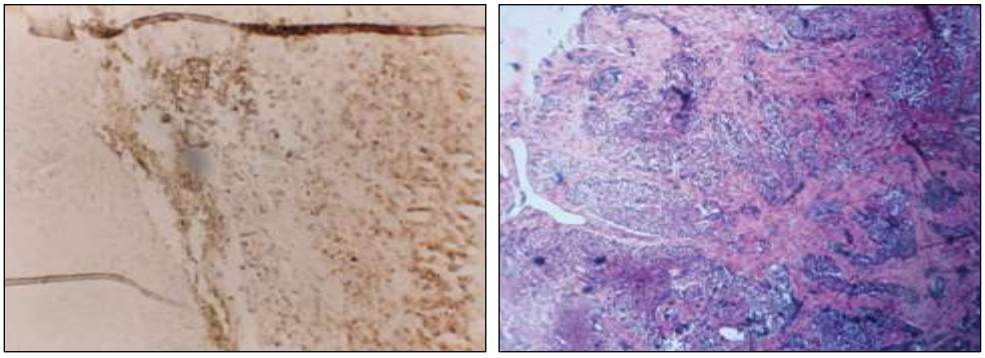
apoptosis and proliferation and found that proteins were markedly decreased in the basal parts of moderate and severe oral epithelial dysplasias when compared with the basal layer of oral epithelium and correlated with a 3-4 fold increase in apoptosis and increased proliferation. From oral epithelium to severe oral epithelial dysplasias, there was an inverse relationship between the bcl-2/bax ratio and apoptosis. Thus, indicating that suppression of bcl-2 may have a role in oral tumourigenesis [25].

Raja Kummoona *et al*. (2007) studied the Bcl-2 expression in a certain histopathologic spectrum of oral tumors and also in the mucosa of the oral cavity of the same patients as control. The results manifested Bcl-2 expression in both squamous cell carcinoma and adenoid cystic carcinoma suggesting that Bcl-2 expression is not linked directly to tumor differentiation but all tumors with active proliferative potential can express this proto oncogene.

Though the Bcl-2 expression was significantly higher in tumor tissue compared with that in normal mucosal tissue, which suggested that the tumor cells are less susceptible to apoptosis compared with cells of normal mucosal tissue expressing a strong correlation between the degree of Bcl-2 expression and grade of malignancy [20].



Bcl-2 expression of moderately differentiated squamous cell carcinoma (moderately positive score 2; x100), and the same photograph below with hematoxylin and eosin staining (x100)

4. Skp-2 (S phase Kinase associated Protein 2)

S-phase kinase-associated protein 2 (Skp2) is a member of the F-box family of substrate-recognition subunits of Skp1-Cullin-F-box ubiquitin-protein ligase complexes which is necessary for p27 ubiquitination and degradation and positively regulates G1- S transition. The importance of G1-S progression in the formation of malignant tumors has been highlighted by the high incidence of aberrations in genes involved in this progression in a wide variety of tumors [26].

Overexpression of Skp-2 may occur in neoplasms. A high level of Skp-2 seems to play an important role in tumorigenesis. Expression of Skp-2 correlates directly with the grade of malignancy in lymphomas and oral squamous cell carcinomas and forced expression of Skp2 in quiescent fibroblasts induces DNA synthesis.

Expression of Skp2 is required for the ubiquitination and subsequent degradation of p27 and Skp2 knock-out cells show high levels of p27 and free cyclin E, polyploidy, and centrosome overduplication. Therefore, a decreased level of p27 expression in human malignant tumors may be caused by increased expression of Skp2, which targets p27 for degradation [26].

Kudo Y *et al*. (2001) stated that Skp2 may play an important role for the development of oral squamous cell carcinoma. Skp2 can be a novel target for OSCC treatment as well as a strong prognostic marker, and the reduction in $p27^{Kip1}$ protein may be brought about by enhancement of its degradation mediated by increased Skp2 protein [27].

Shintani S *et al*. (2003) concluded that overexpression of Skp-2 and Jab 1 is associated with reduction of p27(Kipl) expression and may have a role in the progression of oral squamous cell carcinoma with cervical lymph node metastasis and poor prognosis [28].

Kitajima S *et al*., (2004) suggested that Cks1 (cyclin-dependent protein kinase subunit) overexpression may play an important role for oral squamous cell carcinoma development through Skp2-mediated p27 degradation, and that Cks1 Small interfering RNA (siRNA) can be a novel modality of gene therapy [29].

Harada K *et al*., (2005) revealed that reduced term of survival was related to high levels of Skp2 expression. These results suggested that Skp2 may be a useful prognostic factor in oral squamous cell carcinoma patients [30].

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